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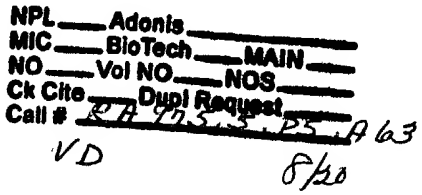

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Nouv Rev Fr Hematol. 1989;31(2):77-84.

Cancer Chemother Biol Response Modif. 1991;12:67-73.

Onkologie. 1991 Feb;14(1):7-12.

Drugs. 1992;44 Suppl 4:1-16; discussion 66-9.

Semin Oncol. 1992 Dec;19(6):639-45.

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CLINICAL REVIEW

Vinorelbine: A novel vinca alkaloid

CINDY TOSO AND CELESTE LINDLEY

Abstract: The chemistry, pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of vinorelbine are reviewed.

Vinorelbine is a semisynthetic vinca alkaloid with a broader spectrum of antitumor activity in vitro than naturally occurring vinca alkaloids have. Vinorelbine shows selective activity against mitotic microtubules. Higher concentrations of vinorelbine relative to vinblastine and vincristine are required to affect axonal microtubules; presumably this accounts for the decreased neurotoxicity of vinorelbine. Vinorelbine is lipophilic and is rapidly distributed into peripheral tissues. It is highly bound to blood components. Vinorelbine is excreted slowly by the fecal route and rapidly by the urinary route. Disposition is characterized by a three-compartment model, high systemic clearance, and a long terminal-phase elimination half-life. In clinical studies, vinorelbine has shown antitumor activity both as a single agent and in combination with cisplatin in patients with non-small-cell lung cancer (NSCLC). Vinorelbine plus cisplatin produces a higher response rate and longer survival than vindesine plus cisplatin, a combination previously found to be superior to best supportive care. Encouraging results for vinorelbine in the treatment of advanced breast cancer, advanced ovarian epithelial cancer, and other tumors have also been observed. The dose-limiting adverse effect of vinorelbine is myelosuppression. Vinorelbine has FDA-approved labeling for use alone or in combination with cisplatin for the first-line treatment of unresectable, advanced NSCLC. The recommended dosage is 30 mg/sq m i.v. weekly administered by either slow i.v. push or i.v. infusion.

Vinorelbine alone or in combination with other antineoplastics has shown activity against NSCLC, advanced breast cancer, and other malignancies. More study is needed to determine whether vinorelbine is superior to best supportive care in patients with NSCLC.

Index terms: Antineoplastic agents; Carcinoma; Dosage; Pharmacokinetics; Toxicity; Vinorelbine tartrate

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The naturally occurring vinca alkaloids vincristine and vinblastine are included in combination chemotherapy regimens for the treatment of many common malignancies. Research to develop semisynthetic derivatives of vinca alkaloids with improved efficacy and reduced toxicity has led to several novel agents. For example, vindesine is a synthetic vinca alkaloid available in Canada and Europe primarily for the treatment of non-small-cell lung cancer (NSCLC). Paclitaxel was later identified as another naturally occurring microtubule inhibitor, although its effect on microtubules differs considerably from that of the other vinca alkaloids.

Vinorelbine is a novel semisynthetic vinca alkaloid with a broader spectrum of activity in vitro and less toxicity than the naturally occurring vinca alkaloids have. Vinorelbine (as the tartrate salt; Navelbine, Glaxo Wellcome) is currently the only antineoplastic agent with FDA-approved labeling for use in the first-line treatment of NSCLC. This article reviews the chemistry, pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of vinorelbine. Clinical trials published in peer-reviewed journals are discussed in detail; abstract data are discussed when deemed to be unique and important. Information for this review was obtained via a MEDLINE search and was supplemented by unpublished literature from Glaxo Wellcome.

Chemistry

Vinca alkaloids have a large dimeric asymmetrical structure composed of a dihydroindole nucleus (vin-

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doline) and an indole nucleus (catharanthine) linked by a carbon–carbon bond. Vinorelbine (3',4'-didehydro-4'-deoxy-C'-norvincaleukoblastine) is a semisynthetic derivative of vinblastine. It is synthesized via a biomimetic pathway between vindoline and catharanthine. Unlike other vinca alkaloids, which differ by substitutions to the vindoline nucleus, vinorelbine has structural modifications of the catharanthine nucleus. It has an eight-membered catharanthine ring rather than the nine-membered ring present in naturally occurring vinca alkaloids. These structural modifications make vinorelbine more lipophilic than other vinca alkaloids. The molecular formula is $C_{45}H_{54}N_4O_8 \cdot (2C_4H_6O_6)$, and the molecular weight is 1079.12.

Pharmacology

Mechanism of action. Vinca alkaloids appear to exert their antitumor activity by binding to tubulin with high affinity.[1] Two types of tubulin, α and β, exist as dimers that polymerize to form microtubules, of which many cellular structures, including the mitotic spindle, are constituted. The cellular functions of microtubules include neurotransmission and mitosis. Vinca alkaloids are cell cycle-specific agents that arrest mitosis by interfering with microtubule assembly and inducing depolarization of microtubules. Like other vinca alkaloids, vinorelbine may also interfere with amino acid, cyclic adenosine 5'-monophosphate, and glutathione metabolism; calmodulin-dependent calcium-transport-adenosinetriphosphatase activity; cellular respiration; and biosynthesis of nucleic acids and lipids.

All vinca alkaloids are thought to have slightly different mechanisms of action due in part to differences in their interaction with microtubule-associated proteins, which are believed to modify the interaction of vinca alkaloids with tubulin.[2] At least two sites of vinca alkaloid fixation on tubulin have been reported: one site with high affinity, which is responsible for depolymerization activity, and one site with low affinity, which induces unwinding of microtubules and spiral formation. Cros et al.[2] found that vinorelbine was as active as vincristine and vinblastine in inducing the assembly of tubulin in vitro but was uniquely inefficient in causing spiral formation. This observation led to the hypothesis that vinorelbine may have a mechanism of action differing slightly from that of other vinca alkaloids and may be less potentially toxic.

Vinorelbine appears to have selective activity against mitotic microtubules. Binet et al.[3] compared the effect of vinorelbine, vinblastine, and vincristine on mitotic and axonal microtubules in postimplantation mouse embryos at the earliest stage of neuronal development. Mitotic microtubule activity appears to be correlated with antitumor activity, while axonal microtubule activity is thought to be correlated with neurotoxicity. At low concentrations (2 μM), vincristine, vinblastine, and vinorelbine inhibited spindle assembly by arresting division at metaphase. At higher concentrations (25 μM), only vinorelbine arrested mitosis at prophase. Depolymerization of axonal microtubules was concentration dependent and occurred at markedly higher concentrations of vinorelbine (40 μM) than of vincristine (5 μM) or vinblastine (30 μM); presumably this accounts for the decreased neurotoxicity of vinorelbine. Further research is needed to describe clearly the interaction of vinorelbine with tubulin and to determine the clinical relevance of this activity.

Drug resistance. Resistance to vinca alkaloids is thought to be mediated primarily by the multidrug resistance (*mdr*) gene.[4] The *mdr* gene is responsible for resistance to several large, hydrophobic, naturally occurring products, such as anthracyclines, epipodophyllotoxins, and vinca alkaloids. Resistance to vinca alkaloids may result from the overexpression of a gene that encodes for a plasma membrane glycoprotein, or P-glycoprotein. The normal function of this protein is the export of cellular toxins. Overexpression of the gene results in enhanced export of vinca alkaloids and similar products from tumor cells. Resistance to drugs that cause microtubule depolymerization can also be due to mutant forms of P-glycoprotein and alterations in tubulin structure. Overexpression of the *mdr* gene usually produces a parallel increase in resistance to all drugs susceptible to multidrug resistance, while mutant forms of the glycoprotein or tubulin may result in resistance to certain agents only.

The exact mechanism of resistance to vinorelbine has not been clearly defined, but the resistance is hypothesized to be mediated largely by the *mdr* gene. Vinorelbine has been reported to exhibit weak cross-resistance with vincristine and vindesine,[5,6] which suggests that a mutant form of glycoprotein or changes in tubulin may be involved in resistance to vinorelbine. There have been no reports describing the use of vinorelbine against either vincristine- or vinblastine-resistant tumors in patients. Thus, the usefulness of vinorelbine in vinca alkaloid-resistant patients remains to be established. Furthermore, although information on cross-resistance of vinorelbine with other drugs affected by the *mdr* gene is lacking, indirect evidence suggests that vinorelbine may be effective in breast cancer patients who have relapsed after treatment with anthracyclines.

Experimental antitumor activity. The antitumor activity of vinorelbine has been studied in vitro and in vivo according to National Cancer Institute Screening Program guidelines.[2] Most of the studies provided for direct comparisons of vinorelbine, vincristine, and vinblastine. At low concentrations (1–10 nM), vinorelbine was active in vitro against 24 human tumor cell lines, including leukemia, NSCLC, SCLC, colon cancer, breast cancer, CNS cancer, and melanoma. Vinorelbine was generally as active as the other vinca

alkaloids against three murine tumor cell lines in vivo: P388 lymphocytic leukemia, B16 melanoma, and M5706 reticulosarcoma. Vinorelbine was more active than vincristine but less active than vinblastine against a fourth murine tumor cell line (L1210 lymphoid leukemia). The activity of vinorelbine was also assessed in several human tumors grafted into nude mice. Vinorelbine was as active as vinblastine against one NSCLC cell line (OG-56), one SCLC cell line (LX-1), and one gastric carcinoma cell line (4-1-ST). Vinorelbine was more active than vinblastine against a second SCLC cell line (QG-90). Other comparative studies showed that vinorelbine was as active as but less toxic than vindesine and superior to vinblastine and vincristine against LC-06, an SCLC cell line. Vinorelbine was the only vinca alkaloid active against L-27, a lung adenocarcinoma cell line. It was also the most active agent against two stomach tumors, ST-4 and ST-40. Vinorelbine–cisplatin and vinorelbine–etoposide showed increased activity without enhanced toxicity against murine leukemia grafts (P388).

Pharmacokinetics

Concentrations of vinorelbine and its metabolites in biological fluids have been determined by measuring total radioactivity, by radioimmunoassay, and by high-performance liquid chromatography (HPLC). Most of the early studies involved the total-radioactivity assay, which measures both unchanged vinorelbine and all metabolites that retain the labeled moiety. The total-radioactivity assay is highly sensitive but lacks the specificity needed in pharmacokinctic studies. Radioimmunoassay was primarily used in animal studies and some early clinical studies. Although radioimmunoassay is more specific than measuring total radioactivity, there is cross-reactivity with metabolites of the vindoline ring structure.[7] Recently, three HPLC methods were developed for analyzing vinorelbine.[7-9] HPLC has complete specificity for the parent drug and allows for measurement of its metabolites. Therefore, clinical studies in which HPLC is used are thought to provide the most valid pharmacokinetic estimates for vinorelbine. These studies are summarized in Table 1.[10-12]

Distribution. Vinorelbine is lipophilic and is rapidly distributed into peripheral tissues. In preclinical studies, animals given radioactively labeled vinorelbine showed rapid and extensive tissue uptake of the drug, consistent with its large volume of distribution.[13] The highest radioactivity counts were found in the spleen, liver, kidneys, lungs, and thymus. Moderate radioactivity was found in the heart and muscle; minimal radioactivity was present in fat, bone marrow, and brain tissue.

Vinorelbine is highly bound to various blood components, especially platelets (78%) and lymphocytes (5%); there is also binding to α_1-acid glycoprotein, albumin, erythrocytes, and lipoproteins. Total binding in serum from 24 cancer patients ranged from 79.6% to 91.2%. The average unbound fraction was 0.135 (range, 0.088–0.204). Binding in whole blood was higher than in serum, reflecting the substantial binding to platelets.[14]

Elimination. The disposition of vinorelbine was assessed by total-radioactivity assay and radioimmunoassay in two cancer patients after intravenous administration of 30 mg/sq m.[15] Samples were also analyzed by HPLC to evaluate the importance of vinorelbine metabolism. Fecal excretion, determined by total-radioactivity assay, accounted for 34% and 58% of elimination of the dose. Fecal excretion occurred slowly, however; the highest fecal excretion values were observed on day 3 (17–25% of the dose). The total-radioactivity assay showed that urinary excretion accounted for 16% and 21% of elimination. Urinary excretion appeared to be rapid, with 61–65% of the total amount excreted within 24 hours, regardless of the assay method. HPLC showed that a mean ± S.D. of 95.2 ± 4.5% of vinorelbine excreted in the urine was in the form of the parent drug. After three weeks of urine and feces collections, total recovery was 50% for one patient and 79% for the other.

In two studies, HPLC was used to investigate the disposition of vinorelbine (Table 1).[10,11] Jehl et al.[10] studied vinorelbine pharmacokinetics in 20 patients with NSCLC. Area under the concentration–time curve (AUC), clearance (CL), and terminal-phase elimination

Table 1.
Summary of Pharmacokinetic Studies of Vinorelbine with High-Performance Liquid Chromatography

			Variable[a]			
Reference	Regimen	No. Pts.	AUC (ng·hr/mL)	CL (L/hr/kg)	$t_{½}$ (hr)	V (L/kg)
10	30-mg/sq m i.v. infusion over 15 min	20	701.2 ± 54.4	1.26 ± 0.09	42.1 ± 4.7	75.6 ± 9.2
11	30-mg/sq m i.v. infusion over 15 min weekly × 8 wk	8	800 ± 350	1.28 ± 0.54	44.7 ± 18.6	47.6 ± 41.9
12	30-mg/sq m i.v. infusion	16	911.4 ± 416.4	0.97 ± 0.40	27.7 ± 15.7	25.4 ± 15.7

[a]Reported as mean ± S.D. AUC = area under the concentration-time curve, CL = clearance, $t_{½}$ = terminal-phase elimination half-life, V = volume of distribution at steady state.

half-life ($t_{½}$) were determined with compartmental calculations. The disposition of vinorelbine was consistent with a three-compartment model. Concentrations decreased rapidly, from 1130 ng/mL at the end of the infusion to 40.7 ng/mL at two hours. Remaining vinorelbine concentrations declined very slowly after 24 hours. A mean ± S.D. of only 10.9 ± 0.7% of the dose appeared in the urine as unchanged drug.

Marquet et al.[11] reported similar results. Eight lung cancer patients received weekly doses of vinorelbine 30 mg/sq m i.v. for eight weeks. Large differences in pharmacokinetic values were noted among the patients. In four patients who were assessed at weeks 1 and 8, significantly higher concentrations were noted at week 1, suggesting time-dependent pharmacokinetics. AUC and CL were not significantly different at the two time points. However, the large variability in pharmacokinetics and the small number of patients may potentially have prevented the detection of a statistically significant difference.

Evidence of time dependence and dose dependence of vinorelbine pharmacokinetics has been found in at least two other studies.[16,17] It is possible that the differences in concentrations merely reflect the drug's high intrinsic clearance, which is subject to considerable interpatient and intrapatient variability. However, the majority of vinorelbine studies had a very narrow dosage range; thus, dose dependence would be difficult to document. Dose-dependent pharmacokinetic behavior may occur with vinorelbine but is unlikely to be a concern given the doses in current clinical use.

These studies indicate that vinorelbine disposition is characterized by a three-compartment model, high systemic CL, and a long terminal-phase $t_{½}$. Urinary excretion of vinorelbine appears to account for less than 15% of a dose. The high CL of vinorelbine is approximately equal to the hepatic blood flow, which is about 1.3 L/hr/kg in humans. Thus, vinorelbine has a high hepatic extraction ratio.

Metabolism. In vitro studies with human hepatic subcellular fractions identified two metabolites of vinorelbine.[18] Subsequently, an HPLC assay specific for vinorelbine and two of its potential metabolites, deacetylvinorelbine and *N*-oxide vinorelbine, was developed.[7] The *N*-oxide derivative appears to be inactive and nontoxic, while the deacetyl derivative shows pharmacologic activity and toxicity similar to those of the parent drug. In a study of single doses of vinorelbine 30 mg/sq m i.v. in 20 patients, *N*-oxide vinorelbine was not detected in serum or urine.[10] No deacetylvinorelbine was recovered in serum, but a small amount was recovered in the urine. Two other structurally unidentified compounds, appearing as peaks in urinary chromatograms, were observed in about half of the patients. Investigation of these compounds in bile was not completed. Therefore, either the metabolic fate of vinorelbine is different in the liver in vivo or the metabolites have different routes of elimination, possibly via the bile.

Biliary excretion. The research in humans, as well as preclinical animal studies, suggests that vinorelbine and its metabolites are excreted in the bile.[13] Leveque et al.[19] investigated the biliary excretion of vinorelbine in pigs. After biliary cannulation, pigs received i.v. doses of vinorelbine 0.5 mg/kg. The excretion of vinorelbine and its metabolites in the bile was assessed by HPLC. Twenty-six percent of the dose was recovered in the bile as unchanged vinorelbine after 48 hours of bile collection. Small amounts of deacetylvinorelbine (<5%) were also found. No glucuronide metabolite of vinorelbine was detected. The investigators did not attempt to identify the *N*-oxide derivative.

Influence of cisplatin on vinorelbine pharmacokinetics. The pharmacokinetics of vinorelbine as a single agent and in combination with cisplatin were investigated to determine whether the increased antitumor activity of the combination results from a pharmacokinetic interaction.[20] Five patients with NSCLC received a single 30-mg/sq m dose of vinorelbine, and four received cisplatin 80 mg/sq m one hour after a 30-mg/sq m vinorelbine dose. Mean CLs (0.90 and 0.87 L/min/sq m) and AUCs (414 and 407 ng·hr/mL) were similar between the groups, suggesting that the pharmacokinetic profile of vinorelbine does not change when cisplatin is administered one hour after a dose of vinorelbine. Therefore, the enhanced antitumor activity of the combination of vinorelbine and cisplatin observed in clinical trials is probably not a consequence of a pharmacokinetic interaction.

Oral vinorelbine. The oral route is under investigation as a method of delivering vinorelbine at continuous low concentrations. Zhou et al.[17] used radioimmunoassay to evaluate the pharmacokinetics of oral vinorelbine in 19 cancer patients. The patients received single weekly doses ranging from 50 to 200 mg/sq m for four weeks. Vinorelbine was absorbed rapidly (time to maximum concentration [t_{max}], 0.9–1.75 hours), and t_{max} did not appear to be dose dependent. A linear relationship existed between the dose and the maximum plasma drug concentration (C_{max}) (range, 70.9–832.6 ng/mL). In some patients, however, C_{max} was reached more slowly when high doses were given. The mean absorption rate constant ranged from 0.85 to 2.42 hr^{-1}.

Rahmani et al.[21] also reported rapid absorption with escalating doses of vinorelbine (50–160 mg) in 15 patients. Vinorelbine was administered weekly by the oral route. Vinorelbine concentration was determined by radioimmunoassay after the first and fourth doses. C_{max} was reached within two hours in 80% of the patients. The mean $t_{½}$ of vinorelbine was 30 hours, which is similar to that observed with i.v. vinorelbine. Food did not appear to affect absorption. The investigators reported no evidence of drug accumulation or autometabolism.

A liquid-filled, soft-gelatin capsule form of vinorelbine was recently developed in an effort to improve oral bioavailability and reduce the potential for toxicity in workers who manufacture the drug. This dosage form was evaluated in 22 cancer patients who received one i.v. dose (30 mg/sq m) and two weekly oral doses (100 mg/sq m).[12] Plasma vinorelbine concentrations were measured with HPLC. The mean absolute bioavailability of the oral formulation was 24%. Thus, oral vinorelbine 100 mg/sq m appears to provide systemic concentrations similar to those achieved with a 30-mg/sq m i.v. dose.

Non-small-cell lung cancer

Lung cancer is the leading cause of death from cancer in men and women over the age of 35 years.[22] NSCLC, including squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma, accounts for approximately 80% of all cases of lung cancer. Treatment depends on the stage of the disease. Surgical resection is the standard treatment for stage I and stage II disease and yields cure rates of approximately 50% and 30%, respectively.[22] However, only about one fourth of patients are diagnosed with one of these stages. Approximately 35% of patients are found to have stage III disease, which includes a heterogeneous group of tumors that are locally advanced but have not yet established distant metastases. The management of stage III disease has been the most controversial and rapidly changing area of lung cancer treatment during the past decade. Patients with stage IIIA disease (potentially resectable) were historically considered poor candidates for surgical resection. However, research has created a role for neoadjuvant therapy before surgery (chemotherapy intended to increase the likelihood of complete resection by destroying local micrometastases and minimizing local surgical seeding of cancer cells) in these patients.[23] Patients with stage IIIB disease (locally advanced, unresectable) are given radiation therapy with or without chemotherapy.

Patients with metastatic (stage IV) disease, who represent approximately 35% of all patients with NSCLC, are given supportive care or chemotherapy. In addition, localized tumors in these patients may be irradiated to relieve symptoms. NSCLC is generally considered resistant to chemotherapy, and the survival time of patients with advanced, unresectable stages of the disease is typically measured in weeks. There are only five currently available agents that can reliably produce responses in more than 15% of patients with advanced NSCLC: ifosfamide, cisplatin, mitomycin, vinblastine, and vindesine.[22] A recent review of new agents for treating NSCLC describes several investigational agents as promising.[24] These include the camptothecin analogues topotecan, irinotecan, and 9-aminocamptothecin; the taxoids paclitaxel and docetaxel; the novel pyrimidine gemcitabine; and the methotrexate analogue edatrexate. Although all these agents are in early clinical development, they appear to produce response rates of 15–50%.

Combination chemotherapy regimens, most often cisplatin based, generally yield higher response rates and longer survival times than single agents in patients with advanced NSCLC. However, their likely impact on overall survival time remains modest and is generally measured in months. The value of combination chemotherapy in advanced NSCLC is consequently debatable. A number of randomized trials have been conducted to compare combination chemotherapy with "best supportive care." Because the results have been widely discordant and the estimates of efficacy unreliable in these small trials, a meta-analysis was recently conducted.[25] Six randomized controlled trials comparing first-line combination chemotherapy with supportive care published in English-language medical journals between 1982 and 1991 were analyzed.[26-31] The meta-analysis confirmed the marginal effect of combination chemotherapy on survival. Overall, chemotherapy was associated with a 24% (95% confidence interval, 13–34%) reduction in the probability of death within the first year, but the effect of treatment was most evident within the first few months and appeared to decrease significantly after six months. The mean potential gain in survival time with combination chemotherapy, compared with supportive care, was approximately 6 weeks (95% confidence interval, 1–10 weeks). Despite these findings, many clinicians choose to treat advanced NSCLC with combination chemotherapy, particularly in young patients with good performance status.

Single-agent therapy. On the basis of Phase I dose-ranging trials, which showed the maximum tolerated dose of vinorelbine to be 30–35 mg/sq m,[32,33] a dosage of 30 mg/sq m i.v. weekly was used in subsequent clinical studies. Table 2 summarizes studies of vinorelbine given as a single agent in patients with NSCLC.[34-39]

Noncomparative studies of i.v. vinorelbine. Only one study of single-agent vinorelbine in NSCLC has been published in full.[34] Seventy-eight patients (75 men and 3 women) with inoperable NSCLC who had not received prior chemotherapy or radiation therapy were enrolled in this multicenter trial. The median age was 62 years (range, 43–75 years) and the median World Health Organization performance status was 1 (0–2). Most of the patients had squamous-cell lung carcinoma, and more than half had stage IV disease. The patients received vinorelbine 30 mg/sq m i.v. once a week. Among 69 evaluable patients, an overall objective response rate of 33% (23 patients) was attained. There was no significant difference in response rates among patients with different stages or histological types of tumors. The overall median survival time was 33 weeks. Eight of the 23 responding patients, includ-

Table 2.
Summary of Studies of Vinorelbine Alone in Previously Untreated Patients with Non-Small-Cell Lung Cancer[a]

Reference	Regimen	No. Evaluable Patients	Response Rate, % (No. PR/No. CR)	Median Duration of Survival (wk)
34	30 mg/sq m i.v. weekly	69	33 (NR)	33
35[b]	20 mg/sq m i.v. weekly	19	26 (5/0)	NR
	25 mg/sq m i.v. weekly	97	32 (31/0)	NR
36[b]	25–30 mg/sq m i.v. weekly (4 pts treated on days 1, 8, 21)	16	37 (6/0)	NR
37[b]	30 mg/sq m i.v. weekly	44	32 (12/2)	NR
38[b]	100 mg/sq m p.o. weekly (80 mg/sq m p.o. weekly if prior radiation)[c]	117	13 (NR)	29
39[b]	30 mg/sq m i.v. weekly	102	12 (NR)	30[d]
	Fluorouracil 425 mg/sq m/day × 5 days + leucovorin 20 mg/sq m/day × 5 days (repeated every 28 days)	47	6 (NR)	22

[a]PR = partial responses, CR = complete responses, NR = not reported.
[b]Reported in abstract form only.
[c]All doses were subsequently reduced by 40 mg/week because of hematologic toxicity.
[d]Significantly different from corresponding value for fluorouracil plus leucovorin group ($p = 0.03$, log-rank test; $p = 0.062$, Cox model).

ing 5 patients with stage IV disease, had a response lasting more than one year.

The objective response rate and response duration observed with single-agent vinorelbine in this study were noteworthy. Other investigators have reported similar activity with single-agent vinorelbine.[35-37] The response rate for single-agent vinorelbine in advanced NSCLC compares favorably with that for other currently available single-agent therapies.

Noncomparative studies of oral vinorelbine. Orally administered vinorelbine is postulated to be better tolerated than combination chemotherapy. In addition, continuous exposure of tumor cells to vinorelbine may produce a greater antitumor effect than intermittent i.v. boluses. Vokes et al.[38] reported in abstract form the preliminary results of a multicenter, open-label, Phase II study of oral vinorelbine in 162 previously untreated patients with stage IV disease. The patients initially received 40-mg soft-gelatin capsules of vinorelbine at a dosage of 100 mg/sq m weekly, or 80 mg/sq m weekly if they had had irradiation. All doses were subsequently reduced by 40 mg because of a high frequency of grade 4 granulocytopenia. The response rate was 13% among 117 patients with measurable disease, and the estimated median survival time was 29 weeks. Hematologic toxicity was common, with rates of grade 3 and grade 4 neutropenia of 37% and 3%, respectively. Nausea (72% of patients), vomiting (62%), and diarrhea (55%) also occurred frequently. The substantial hematologic and gastrointestinal toxicity of oral vinorelbine seen in this study contradicts the notion that oral vinorelbine is better tolerated.

The intended oral dosage of vinorelbine in this study (80–100 mg/sq m weekly) appears to be appropriate in the context of previous estimates of bioavailability derived from pharmacokinetic studies (approximately 24%). However, a reduction in the dosage was necessary because of hematologic toxicity. This raises questions about the validity of the bioavailability estimates.

Comparative studies. The only comparative study involving single-agent vinorelbine in NSCLC was published in abstract form.[39] This multicenter, randomized (2:1) trial compared vinorelbine 30 mg/sq m weekly against fluorouracil 425 mg/sq m/day for five days plus leucovorin 20 mg/sq m/day (as the calcium salt) for five days repeated every 28 days to determine the impact on stage IV disease. Two hundred eleven previously untreated patients were studied; 185 had measurable disease. The median survival time for the entire group was 25 weeks. An intention-to-treat analysis revealed a survival advantage ($p = 0.03$, log-rank test; $p = 0.062$, Cox model) in the patients who received vinorelbine (median survival time, 30 weeks) over the patients who received fluorouracil plus leucovorin (22 weeks). The objective response rates did not differ significantly between the vinorelbine group (12%) and the fluorouracil plus leucovorin group (6%). However, the rate of response to vinorelbine was considerably lower than observed in other single-agent studies (approximately 30%) and cannot be explained by the limited data presented in the abstract.

Quality of life (QOL) in the two groups was assessed with a modified version of the Southwest Oncology Group QOL questionnaire. The instrument assessed role functioning, physical functioning, symptom distress, and global QOL. No between-group differences were observed over the study period for any of the QOL dimensions. QOL was not adversely affected by vinorelbine. The vinorelbine group seemed to show less deterioration of symptoms than the other group. Hematologic toxicity was the most common adverse effect and occurred more frequently with vinorelbine. More than half (53%) of the vinorelbine recipients had grade 3 or 4 neutropenia. Nonhematologic toxicities

included injection-site reactions, which were much more common with vinorelbine (38% versus 1%), constipation, mild nausea, and mild neurotoxicity.

FDA's Oncology Drugs Advisory Committee questioned the statistical tests used to compare survival times in the two groups. The difference was significant ($p = 0.03$) when analyzed by the log-rank test but not ($p = 0.062$) when analyzed by the proportional hazards model, which accounts for several prognostic variables. Regardless of which statistical test is used, the clinical significance of the modest survival advantage (eight weeks) is likely to be less than remarkable. Furthermore, the validity of comparing vinorelbine with fluorouracil plus leucovorin is debatable, since that combination has questionable activity against NSCLC.

Combination therapy. *Vinorelbine plus cisplatin.* Vinorelbine plus cisplatin has been compared with cisplatin plus vindesine in the treatment of NSCLC (Table 3).[40,41] Cisplatin plus vindesine was considered the standard against which to compare other regimens because the combination previously showed a survival advantage over best supportive care in a large multicenter trial in Canada.[31] Thus, it was deemed inappropriate to compare vinorelbine plus cisplatin directly with best supportive care, and an indirect comparison was performed. An initial Phase I–II study was designed to assess tolerance of the combination of vinorelbine and cisplatin.[40] Thirty-two previously untreated patients (27 men and 5 women) with inoperable NSCLC were enrolled. Cisplatin was administered to all the patients at a dose of 120 mg/sq m on day 1, day 29, and then every six weeks. Vinorelbine was given at three successively higher dosages: 20 mg/sq m weekly in 9 patients, 25 mg/sq m weekly in 6 patients, and 30 mg/sq m weekly in 17 patients. Among 30 evaluable patients there were 0, 2, and 5 objective responses in the groups given vinorelbine 20, 25, and 30 mg/sq m, respectively. The median survival time was 11 months. The combination regimen was well tolerated.

Thus, the Phase I–II study demonstrated the feasibility of giving high-dose cisplatin combined with vinorelbine 30 mg/sq m weekly. Furthermore, the response rate justified a Phase III trial of vinorelbine alone versus vinorelbine plus cisplatin versus vindesine plus cisplatin.[41] Previously untreated patients with advanced NSCLC were randomly assigned to receive vinorelbine 30 mg/sq m weekly ($n = 206$); vinorelbine 30 mg/sq m weekly plus cisplatin 120 mg/sq m on day 1, day 29, and then every six weeks ($n = 206$); or vindesine sulfate 3 mg/sq m weekly for six weeks and then every two weeks plus cisplatin as in the vinorelbine plus cisplatin group ($n = 200$). The vindesine plus cisplatin regimen was identical to that used in the Canadian trial that showed its superiority to best supportive care.[31] Ninety percent of the patients were men; their median age was 60 years (range, 30–75 years), and their median WHO performance status was 1 (0–2). Squamous-cell carcinoma was the most common histological type, and more than half the patients had metastatic disease.

An objective response was attained in 120 of 574 evaluable patients. The response rates were 14%, 30%, and 19% in the vinorelbine, vinorelbine plus cisplatin, and vindesine plus cisplatin groups, respectively. The response to vinorelbine plus cisplatin was significantly greater than the response to vindesine plus cisplatin or vinorelbine alone. Rates of response to vinorelbine alone and to vindesine plus cisplatin did not differ significantly. The response rate of 14% for vinorelbine alone is remarkably lower than the 30% response rate noted in other single-agent studies[34-37] but consistent with the 12% response rate reported by O'Rourke.[39] Median survival time was significantly longer in the vinorelbine plus cisplatin group (40 weeks) than in the vindesine plus cisplatin (32 weeks) and vinorelbine (31 weeks) groups. The response rate (19%) and median survival time (32 weeks) for vindesine plus cisplatin are consistent with those reported in the Canadian study (25.3% and 32.6 weeks).[31] Myelosuppression was the most common adverse effect and was significantly worse in the vinorelbine plus cisplatin group than in the other two groups. Grade 3 or 4 neutropenia occurred in 53%, 79%, and 48% of the patients in the vinorelbine, vinorelbine plus cisplatin, and vindesine plus cisplatin groups, respectively. Neurotoxicity occurred significantly more frequently in the vindesine plus cisplatin group than in the other two groups. Grade 3 or 4 neurotoxicity was observed in 9%, 7%, and 17% of the patients in the vinorelbine, vinorelbine plus cisplatin, and vindesine plus cisplatin groups, respectively. Thus, vinorelbine plus cisplatin produced a longer survival time and higher response rate than vindesine plus cisplatin or vinorelbine alone. In addition, neurotoxicity was less common in recipients of vinorelbine plus cisplatin than in vindesine plus cisplatin recipients.

Other investigators have compared vinorelbine alone with vinorelbine plus cisplatin in patients with NSCLC.[42,43] Comparative studies have yielded conflicting results (Table 3). One study demonstrated a significantly higher response rate for the combination regimen than vinorelbine alone (48% versus 17%), but similar survival times.[42] Another study showed similar response rates for the combination regimen and vinorelbine alone.[43] Reasons for the inconsistency cannot be determined, at least not until the full report is published. In addition, although the Phase III trial by Le Chevalier et al.[41] showed an improved response rate for the combination regimen, the response rate for single-agent vinorelbine (14%) was far lower than that observed in many single-agent studies (approximately 30%). It is, therefore, difficult to determine the magnitude of the benefit obtained by adding cisplatin to vinorelbine therapy.

Vinorelbine plus other agents. Investigations of vinorel-

Table 3.
Summary of Studies of Combination Therapies Involving Vinorelbine in Previously Untreated Patients with Non-Small-Cell Lung Cancer[a]

Reference	Regimen	No. Evaluable Patients	Response Rate, % (No. PR/No. CR)	Median Duration of Survival (wk)
40	Cisplatin 120 mg/sq m i.v. on days 1 and 29, then every 6 wk, + vinorelbine 20–30 mg/sq m i.v. weekly	30	Vinorelbine 20 mg/sq m: 0 Vinorelbine 25 mg/sq m: 33 (2/0) Vinorelbine 30 mg/sq m: 29 (5/0)	44
41	Vinorelbine 30 mg/sq m i.v. weekly	199	14 (NR)	31
	Vinorelbine 30 mg/sq m i.v. weekly + cisplatin 120 mg/sq m i.v. on days 1 and 29, then every 6 wk	192	30 (NR)[b]	40[b]
	Vindesine sulfate 3 mg/sq m i.v. weekly × 6 wk, then every 2 wk + cisplatin 120 mg/sq m i.v. on days 1 and 29, then every 6 wk	183	19 (NR)	32
42[c]	Vinorelbine 30 mg/sq m i.v. weekly	104	17 (NR)	32
	Vinorelbine 30 mg/sq m i.v. on days 1, 8, and 15 + cisplatin 80 mg/sq m i.v. on day 1 (repeated every 21 days)	104	48 (NR)[d]	33
43[c]	Vinorelbine 30 mg/sq m i.v. weekly	25	32 (NR)	NR
	Vinorelbine 30 mg/sq m i.v. weekly + cisplatin 100 mg/sq m i.v. (repeated every 4 wk)	27	33 (NR)	NR
44	Vinorelbine 25 mg/sq m i.v. on days 1 and 8 + epirubicin HCl 50–90 mg/sq m i.v. with or without filgrastim (repeated every 21 days)	Epirubicin 50 mg/sq m: 3 Epirubicin 60 mg/sq m: 6 Epirubicin 75 mg/sq m: 3 Epirubicin 90 mg/sq m: 6	0 0 33 (1/0) 33 (2/0)	NR NR NR NR
45[c]	Vinorelbine 18–20 mg/sq m i.v. on days 1 and 8 + fluorouracil 480–600 mg/sq m/day i.v. by CI on days 1–4 + leucovorin 400–600 mg/sq m/day i.v. on days 1–4 + cisplatin 100 mg/sq m i.v. on day 1 (repeated every 21 days)	54	46–65 (25/3)	NR
49[c]	Vinorelbine 20 mg/sq m i.v. on days 1 and 5 + fluorouracil 800 mg/sq m/day i.v. by CI on days 2–5 + leucovorin 100 mg p.o. q 4 hr on days 1–5 + cisplatin 100 mg/sq m/day i.v. on day 1 (repeated every 21–28 days)	16	25 (3/1)	NR
47[c]	Vinorelbine 20 mg/sq m i.v. weekly + ifosfamide 2 g/sq m i.v. on days 1–3 + mesna (repeated every 28 days)	18	56 (4/6)	47
48[c]	Vinorelbine 25 mg/sq m i.v. on days 1 and 8 + ifosfamide 2 g/sq m i.v. on days 1–3 + mesna (repeated every 3 wk)	20	40 (8/0)	42

[a]PR = partial responses, CR = complete responses, NR = not reported, CI = continuous infusion.
[b]Significantly different from corresponding values for vinorelbine alone and vindesine plus cisplatin ($p < 0.05$).
[c]Reported in abstract form only.
[d]Significantly different from corresponding value for vinorelbine alone ($p < 0.0001$).

bine combined with other antineoplastic agents in patients with NSCLC are ongoing. Preliminary reports suggest promising results with epirubicin–vinorelbine,[44] fluorouracil–leucovorin–vinorelbine–cisplatin,[45,46] and ifosfamide–vinorelbine (Table 3).[47,48]

Small-cell lung cancer

Jassem et al.[49] conducted a Phase II study of vinorelbine in previously treated patients with SCLC. Twenty-five patients (19 men and 6 women) with progressive, recurrent SCLC received vinorelbine 30 mg/sq m weekly. A modest 16% partial response rate (4 of the 25 patients) was achieved. The response lasted 9.5 weeks in one patient, 16 weeks in another patient, and 17 weeks in the other two patients. The most common toxic effect was leukopenia, which occurred in 80% of the patients (grade 3 or 4 leukopenia occurred in 32%). Neurotoxicity, primarily paresthesia, was observed in 24% of the patients. Local skin reactions occurred in five patients, and one had grade 3 phlebitis.

The 16% response rate is similar to those reported for other single agents, such as etoposide (20%) and teniposide (15–25%), when given as second-line therapy.[50,51] Conversely, both etoposide and teniposide as first-line therapies have been very active (response rates of 60% and 90%, respectively).[50,52] There are no published reports of vinorelbine as first-line therapy in patients with SCLC. Thus, it is unclear how vinorelbine rates against etoposide and teniposide as a treatment for SCLC.

Advanced breast cancer

Vinorelbine has been extensively investigated in patients with breast cancer. The majority of the published trials have been Phase II trials focusing on the safety and efficacy of single-agent vinorelbine in patients with advanced disease. To date, six trials have been published in full and at least nine in abstract form. Inclusion and exclusion criteria and reporting varied markedly among the trials. The results of studies published in full are described below. Table 4 summarizes published reports and abstracts describing studies of single-agent vinorelbine in previously treated[53-62] and previously untreated[59,63-67] advanced breast cancer. Only one preliminary report (in abstract form) has described a comparison of single-agent vinorelbine with another active agent (melphalan) for advanced breast cancer.[62]

First-line combination chemotherapy produces an objective response in approximately two thirds of patients with metastatic breast cancer. However, responses typically last less than one year, and complete responses occur in less than 25% of patients.[68] The response to second-line chemotherapy is generally less impressive. Few antineoplastic agents can produce an objective response in more than 20% of previously treated patients. Thus, there is a great need to identify novel agents with improved, sustained activity in previously treated patients with advanced breast cancer.

Single-agent therapy. *Previously treated patients.* Vinorelbine was first evaluated as a treatment for advanced breast cancer by Canobbio et al.[53] Twenty-six patients with advanced, measurable breast cancer entered the Phase II study. Patients previously treated with vinca alkaloids or more than one chemotherapy regimen were excluded. Fifteen patients had received prior chemotherapy (adjuvant therapy, 10; palliative therapy, 5), and six patients had received prior palliative hormonal therapy either alone or in combination with chemotherapy. Nineteen patients had not received prior chemotherapy for metastatic disease, and six of these patients had received vinorelbine as first-line therapy because they were not candidates for hormonal therapy or they refused other chemotherapy. All patients received vinorelbine 30 mg/sq m weekly.

Of the 24 evaluable patients, 11 (46%) had an objective response, including 5 with complete responses and 6 with partial responses. An overall response rate of 53% (10 of 19 patients) was attained in individuals previously not given chemotherapy for metastatic disease. The median response duration was 22 weeks (range, 9–41 weeks). High activity was noted in soft tissue (skin and lymph nodes) and visceral (lung and liver) metastatic sites, where response rates of 93% and 50%, respectively, were observed. No responses were observed in bone sites. Leukopenia was the dose-limiting adverse effect but was rapidly reversible and manageable. Neurotoxicity, manifested primarily as

Table 4.
Summary of Studies of Vinorelbine Alone in Patients with Advanced Breast Cancer[a]

Reference	Regimen	No. Evaluable Patients	Response Rate, % (No. PR/No. CR)	Median Duration of Response (wk)
Previously Treated Patients				
53[b]	30 mg/sq m i.v. weekly	24	46 (6/5)	22
54	30 mg/sq m i.v. weekly	33	30 (8/2)	14
55	20–25 mg/sq m i.v. weekly	67	36 (21/3)	29
56[b]	30 mg/sq m i.v. weekly	38	24 (7/2)	14
57[b]	30 mg/sq m i.v. weekly	30	20 (6/0)	≥16
58[b]	30 mg/sq m i.v. weekly	13	38 (5/0)	NR
59[b]	30 mg/sq m i.v. weekly	41	17 (6/1)	NR
60[b]	20–25 mg/sq m i.v. weekly	65	37 (21/3)	20
61[b]	80–100 mg/sq m p.o. weekly	96	11 (11/0)	NR
62[b]	30 mg/sq m i.v. weekly	115	15 (NR)	12[c]
	Melphalan 25 mg/sq m i.v. every 4 wk	64	9 (NR)	8
Previously Untreated Patients				
63	30 mg/sq m i.v. weekly	145	41 (50/10)	34
64	30 mg/sq m i.v. weekly	44	41 (15/3)	36
65	130 mg p.o. weekly	15	0	. . .
59[b]	30 mg/sq m i.v. weekly	65	40 (16/10)	NR
66[b]	30 mg/sq m i.v. weekly	63	44 (25/3)	17
67[b]	30 mg/sq m i.v. weekly	47	51 (NR)	NR

[a]PR = partial responses, CR = complete responses, NR = not reported.
[b]Reported in abstract form only.
[c]Reported as time to disease progression. Significantly different from corresponding value for melphalan group ($p = 0.03$, log-rank test).

constipation and myalgia, occurred in approximately one third of the patients. Most neurotoxicity was mild to moderate (grade 1 or 2), except for one case of grade 3 constipation secondary to paralytic ileus. Venous pain during injection was noted in one third of the patients.

The response rate for vinorelbine observed in this Phase II study was similar to those seen with anthracyclines and paclitaxel, which are considered the most active single agents in patients with breast cancer. However, although this study population was classified as previously treated, 10 of the 15 patients who had had prior chemotherapy received it as an adjuvant, and patients previously treated with other vinca alkaloids or more than one chemotherapy regimen were excluded. Given the limited prior therapy of the patients, it may be more appropriate to consider the population as previously untreated. Thus, the study did not properly assess vinorelbine's activity as conventional second-line therapy.

The activity of vinorelbine in heavily pretreated breast cancer patients was assessed by Extra et al.[54] Thirty-three patients with metastatic disease who had previously received at least one chemotherapy regimen entered the study (the median number of previous regimens was six [range, 2–8]). Vinorelbine was administered weekly at a dose of 30 mg/sq m. Ten (30%) of 33 evaluable patients achieved an objective response (eight partial responses and two complete responses). Few agents tested thus far have demonstrated similar activity in a comparable patient population. The median response duration was 14 weeks (range, 8–52 weeks). Myelosuppression was frequent, with grade 3 or 4 neutropenia occurring in more than half the patients. Grade 1 or 2 neuropathy was observed in 20–35% of the patients. Other important adverse effects included grade 1 or 2 nausea and vomiting and grade 1 or 2 alopecia.

Gasparini[55] described the effects of vinorelbine in 67 patients (median age, 60 years [range, 41–77]) with advanced breast cancer, 25% of whom had received one chemotherapy regimen for metastatic disease, 55% had received two regimens, and 20% had received three or more regimens. Vinorelbine was administered beginning at 20 mg/sq m given by 60-minute i.v. infusion weekly; the dose was increased to up to 25 mg/sq m if the first four courses were well tolerated. Treatment was continued until the disease progressed.

Complete responses were reported in 3 patients (4%) and partial responses in 21 patients (31%), for an overall response rate of 36%. Stable disease was reported in 20 patients (30%) and disease progression in 23 patients (34%). The median dose given was 63% of the intended dose of 25 mg/sq m; 51% of the patients received 50–75% of the intended dose. Myelosuppression was the most common adverse effect, with grade 3 or 4 granulocytopenia reported in 37% of the patients. Chemical phlebitis (grade 2 or 3) was reported in 22% of the patients, two thirds of whom required placement of a central venous line so that they could receive further infusions of vinorelbine. Other nonhematologic toxicities included moderate alopecia, constipation, and reversible peripheral neuropathy.

An important finding was that vinorelbine was active in patients previously treated with anthracyclines. This apparent lack of cross-resistance makes vinorelbine promising for second-line therapy in patients who progress after treatment with cyclophosphamide, methotrexate, and fluorouracil (CMF) or anthracyclines. The response rate of 36% in previously treated patients is consistent with the results of Extra et al.[54] and others. The study showed quite clearly the myelosuppressive effects of vinorelbine in heavily pretreated elderly women. In addition, the venous irritation reported to accompany the one-hour infusion is noteworthy.

There has been only one report of a comparative study involving single-agent vinorelbine in advanced breast cancer; the results were published in abstract form.[62] In this multicenter trial, i.v. vinorelbine was compared with i.v. melphalan in anthracycline-resistant patients. Objective response rates (15% versus 9%) and median survival times (35 versus 31 weeks) were similar in the vinorelbine and melphalan groups, but the time to disease progression (12 versus 8 weeks; $p = 0.03$, log-rank test) and the time to treatment failure (13 versus 8 weeks, $p < 0.01$) favored vinorelbine.

Table 4 illustrates the highly variable response rates (11–46%) for vinorelbine as second-line therapy. Since many of these studies were published only in abstract form, no explanation for the variability is discernible. Additional comparative studies are needed to define vinorelbine's role in relapsed advanced breast cancer.

Previously untreated patients. One hundred fifty-seven patients with advanced breast cancer entered a multicenter study to evaluate vinorelbine as first-line therapy.[63] Forty-three percent had received prior adjuvant chemotherapy; 68% of those patients had been given anthracycline-based adjuvant therapy. The patients were given vinorelbine 30 mg/sq m weekly. The median number of vinorelbine treatments was 9 (range, 1–53); the average dose given was 69% of the intended dose. The overall response rate was 41% (60 of 145 evaluable patients); 50 had a partial response and 10 a complete response. The response rate was highest for skin sites (70%) and lymph node sites (67%). The response rate for bone sites was 27% (3 of 11 patients). For patients previously treated with anthracycline-based adjuvant therapy, the response rate was 39% (17 of 44 patients). The median response duration was 34 weeks. The median survival time for all the patients was 18 months. The most frequent adverse effect was hematologic toxicity. Grade 3 or 4 granulocytopenia was observed in 73% of the patients during at least one cycle. Anemia and

thrombocytopenia were uncommon. Nonhematologic toxicity included mild nausea and vomiting and constipation. Eight percent of patients who received vinorelbine without central venous access developed phlebitis that necessitated placement of a central venous line.

Romero et al.[64] recently reported the results of another Phase II study evaluating the efficacy and toxicity of vinorelbine as first-line therapy for metastatic breast cancer. Forty-five women were included. Half of the patients (49%) had received prior adjuvant chemotherapy, 44% had received prior hormonal therapy, and 69% had received previous adjuvant radiation therapy. Vinorelbine was given as a 30-mg/sq m i.v. infusion over one hour, repeated weekly. Venous flushing with 250 mL of 0.9% sodium chloride injection followed vinorelbine administrations.

An objective response was observed in 18 (41%) of 44 evaluable women. There were three complete responses (7%) and 15 partial responses (34%). Fourteen patients (32%) had no change, and 12 (27%) had disease progression. The median response duration was 9 months (range, 1–15 months); the median duration of survival has not yet been determined. A response rate of 67% was achieved in patients with soft tissue disease (six of nine patients); the response rate for patients with bone metastases was 33% (5 of 15). Of 19 patients previously treated with doxorubicin-containing adjuvant chemotherapy, 7 (37%) responded to vinorelbine. The dose-limiting adverse effect of vinorelbine was myelosuppression. Leukopenia occurred in 35 patients (78%); grade 3 or 4 leukopenia was observed in 16 patients (36%). The leukopenia did not appear to be cumulative. Documented infection developed in four patients (9%). Thrombocytopenia was uncommon (13% of patients); no episodes of bleeding were noted. Grade 2 or 3 anemia occurred in 15 patients (33%); the anemia appeared to be a cumulative effect. Nonhematologic adverse effects included phlebitis in 19 of 29 patients without central venous lines, peripheral neuropathy, constipation, myalgia, elevated liver enzymes, nausea, vomiting, diarrhea, stomatitis, alopecia, and mild asthenia.

These results confirm the value of vinorelbine for first-line therapy in advanced breast cancer. Other investigators have reported a similar efficacy of vinorelbine in advanced breast cancer.[59,66,67] Table 4 shows that the overall response rate for single-agent i.v. vinorelbine in previously untreated advanced breast cancer is 40–50%; the complete response rate is 2–15%. Response rates in patients previously treated with anthracycline-based adjuvant chemotherapy (33–38%) suggest that prior exposure to anthracyclines does not predict a poorer response to vinorelbine. The activity of vinorelbine appears to be comparable to those of doxorubicin and paclitaxel, but directly comparative studies are needed.

Continuous infusion. During the past two decades, continuous infusions of phase-specific antineoplastic drugs have been tried in the belief that constant exposure of cancer cells to these agents would decrease adverse effects and increase overall dose intensity. The cytotoxicity of vinca alkaloids has been reported to be critically dependent on both drug concentration and the duration of exposure.[69] Several trials involving continuous infusion of vinca alkaloids showed, in many instances, increased activity with acceptable toxicity.[69-71] The use of continuous infusions of vinca alkaloids in previously untreated patients has been advocated on the grounds that continuous infusion overcame clinical drug resistance in some cases that were refractory to bolus treatment with a vinca alkaloid.[72]

Toussaint et al.[73] conducted a Phase I–II study of vinorelbine administered by continuous i.v. infusion to patients with advanced breast cancer. Vinorelbine was given as an initial i.v. bolus injection (8 mg/sq m) on day 1, followed by a four-day continuous i.v. infusion to be repeated every 21–28 days. Five different 24-hour dosages of continuously infused vinorelbine were investigated, ranging from 5.5 to 10 mg/sq m. The drug was administered to all the patients through a central venous line.

Sixty-four patients completed the trial. The objective response rate of 36% was similar to that reported in previous trials. The median response duration was six months. More interestingly, there was a relationship between dose intensity and objective response rate, with an overall response rate of 13% (2 of 15 patients) for 8–10 mg/sq m/week; 35% (11/31) for 10–12 mg/sq m/week, and 56% (10/18) for 12–14.5 mg/sq m/week. Similarly, a relationship between dose intensity and grade 3 or 4 neutropenia was observed. Two new adverse effects occurred with the continuous-infusion schedule: a moderate (42% of patients) to severe (14%) asthenia lasting two days to two weeks, with a cumulative trend, and low to moderate fever (15%). A causal relationship between the fever and the continuous infusion was likely, since the fever started 24–48 hours into the four-day infusion and resolved shortly after the infusion ended. The hematologic toxicity encountered with the continuous infusion was similar to that seen with the weekly bolus-injection schedule.

This study confirmed the high activity of vinorelbine against advanced breast cancer while proving the feasibility of administering the drug by continuous i.v. infusion. Such a dosage schedule may increase the therapeutic index of vinorelbine and further underscores the importance of dose intensity in obtaining the desired antitumor response.

The potential for oral vinorelbine to be as effective as continuously infused vinorelbine without the attendant demands and risks makes investigation of an oral dosage formulation even more attractive.

Oral vinorelbine. In a Phase II study, Queiber et al.[65] sought to evaluate the efficacy and adverse effects of

Table 5.
Summary of Studies of Combination Therapies Involving Vinorelbine in Patients with Advanced Breast Cancer[a]

Reference	Regimen	Previous Chemotherapy	No. Evaluable Patients	Response Rate, % (No. PR/No. CR)	Median Duration of Response (wk)
74	Vinorelbine 30 mg/sq m i.v. every 3 wk + mitomycin 15 mg/sq m i.v every 6 wk	Yes	34	35 (10/2)	24
75[b]	Vinorelbine 25 mg/sq m i.v. on days 1 and 8 + doxorubicin HCl 50 mg/sq m i.v. on day 1 (repeated every 21 days)	NR	45	34 (NR)	12
	Fluorouracil 500 mg/sq m i.v. + doxorubicin HCl 50 mg/sq m i.v. + cisplatin 500 mg/sq m i.v. (repeated every 21 days)	NR	41	35 (NR)	16
76[b]	Vinorelbine 25 mg/sq m i.v. on days 1 and 8 + mitoxantrone HCl 12 mg/sq m i.v. on day 1 (repeated every 21 days)	No	32	56 (10/8)	NR
77[b]	Vinorelbine 30 mg/sq m i.v. on days 1 and 5 + fluorouracil 750 mg/sq m i.v. on days 1 and 5 (repeated every 3 weeks)	No	63	67 (32/10)	36
78[b]	Mitoxantrone HCl 10 mg/sq m i.v. on day 1 + vinorelbine 30 mg/sq m i.v. on day 3 + ifosfamide 2 mg/sq m i.v. on days 1–2 + mesna (repeated every 28 days)	Yes	29	41 (11/1)	NR
79[b]	Mitoxantrone HCl 12 mg/sq m on day 1 + vinorelbine 12 mg/sq m i.v. on day 2 + ifosfamide 1.2 mg/sq m on days 1–3	Yes	38	37 (14/0)	36
	Above regimen + sargramostim 5 µg/kg s.c. on days 5–15	Yes	41	44 (18/0)	40
83[b]	Vinorelbine 25 mg/sq m i.v. on days 1 and 8 + doxorubicin HCl 50 mg/sq m i.v. on day 1 (repeated every 21 days)	No	50	54 (21/6)	NR

[a]PR = partial responses, CR = complete responses, NR = not reported.
[b]Reported in abstract form only.

oral vinorelbine in patients with metastatic breast cancer. A hard-gelatin capsule with a reported average bioavailability of 45% was used in this study. Vinorelbine was administered at a dosage of 130 mg weekly; treatment was delayed in the event of prolonged hematologic toxicity. Seventeen patients with advanced breast cancer who had a positive hormone-receptor status or a disease-free interval of more than 24 months were included. Patients previously given chemotherapy for metastatic disease were excluded.

The treatment was administered for a median of 11 weeks (range, 3–24 weeks), and total doses of vinorelbine ranged from 130 to 3120 mg. No objective responses were observed in the 15 evaluable patients, and there was substantial toxicity. Leukopenia was the most common hematologic adverse effect (grade 1 or 2, 24%; grade 3 or 4, 18%). Mild anemia occurred in four patients (24%). Gastrointestinal toxicity was also common and included loss of appetite, nausea, vomiting, and diarrhea. Neurotoxicity was infrequent and generally mild. The reason for the lack of response in conjunction with the toxicity is unclear. Vokes et al.[38] reported similar adverse effects of the soft-gelatin capsule in patients with NSCLC; dosage reductions were required. The pharmacokinetic disposition of oral vinorelbine requires further evaluation.

Combination therapy. The activity of single-agent vinorelbine as first- and second-line therapy for advanced breast cancer has led to investigations of regimens combining vinorelbine with other antineoplastics. Several preliminary reports are summarized in Table 5.[74-80] Although the results are preliminary, it appears that vinorelbine in combination with other active agents achieves a response in at least 30% of previously treated patients and compares favorably to standard three-drug regimens.

Advanced ovarian epithelial cancer

George et al.[81] evaluated vinorelbine 30 mg/sq m weekly in 38 women with ovarian epithelial cancer who had relapsed or whose disease was progressing despite chemotherapy. The patients had not previously received vinca alkaloids and had not undergone more than two prior courses of chemotherapy. All the patients had had at least one surgical procedure and had been given at least one cisplatin regimen; 10 had had

prior radiation therapy. Thirty-seven and 32 patients were evaluable for toxicity and clinical response, respectively. An objective response rate of 16% was achieved: There was one complete remission and one partial response. Myelosuppression was the dose-limiting adverse effect. Grade 3 or 4 granulocytopenia was observed in 26 patients and grade 3 or 4 thrombocytopenia in 4 patients. No septic or bleeding complications occurred. Nonhematologic adverse effects were nausea, vomiting, alopecia, constipation, peripheral neurotoxicity, and local reactions.

The objective response rate attained with vinorelbine in this group of heavily pretreated patients is encouraging. A preliminary report by Pinel et al.[82] also noted substantial activity of vinorelbine plus altretamine as second-line or later therapy for advanced ovarian cancer. Further study is needed to establish the role of vinorelbine as a treatment for ovarian cancer.

Hodgkin's disease

Vinorelbine as a treatment for Hodgkin's disease is in early stages of investigation. Benchekroun et al.[83] studied 32 patients (20 men and 12 women) with previously untreated Hodgkin's disease. Half of the patients had stage IV disease; histologic types 2 and 3 were the most common (69%). Vinorelbine was administered weekly at a dose of 30 mg/sq m i.v. A clinical examination was conducted on day 15 to determine if vinorelbine treatment should be continued; the drug was discontinued if there were no signs of a response. One week after the fourth injection, a new disease assessment was made, and the MOPP/ABVD protocol (mechlorethamine, vincristine, procarbazine, and prednisone alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine) was started. Remission was complete in 1 patient and incomplete in 27 patients; 3 patients had a minor response. An objective response was apparent after an average of 10 days (range, 6–21 days). The treatment was well tolerated. Neutropenia was the most common complication, occurring in 17 patients. No neurotoxicity was observed.

Encouraging preliminary results have been obtained with mitoguazone, ifosfamide, vinorelbine, and etoposide (MINE) as salvage therapy for refractory or relapsed Hodgkin's disease. Ferme et al.[84] reported an objective response rate of 81% in 32 patients. The authors suggested that MINE is an effective salvage therapy for relapsed Hodgkin's disease before bone marrow transplantation.

Head and neck tumors

Gebbia et al.[85] investigated the antitumor activity and toxicity of vinorelbine in 24 patients with recurrent or metastatic squamous-cell head and neck carcinoma. All but two patients had received previous treatment (surgery, 12%; radiation therapy, 8%; and fluorouracil plus cisplatin, 6%). Vinorelbine was administered i.v. at 20 mg/sq m weekly for the first group of three patients and then increased by 5 mg/sq m/week for subsequent groups. However, the dosage could not be increased beyond 30 mg/sq m weekly because of hematologic toxicity. Thus, 25 mg/sq m/week was given to the remainder of the patients. A partial response (median duration, 5.8 months) was observed in 5 (22%) of the 23 evaluable patients. No responses were observed in the patients previously given chemotherapy. Seven patients had no change, and 11 had disease progression.

The activity of single-agent vinorelbine in recurrent or metastatic squamous-cell head and neck carcinoma encouraged investigation of combinations with fluorouracil and cisplatin. The same investigators reported preliminary results of a study of vinorelbine (25 mg/sq m on days 2 and 8) plus cisplatin (80 mg/sq m on day 1) plus fluorouracil (600 mg/sq m on days 2–5) in patients with recurrent or metastatic disease.[86] Of 18 evaluable patients enrolled thus far, 2 patients achieved a complete response and 9 a partial response; 5 patients showed no change, and 2 had disease progression.

Other malignancies

In preliminary investigations, vinorelbine has had little or no activity against advanced renal-cell carcinoma[87-89] and germ-cell tumors.[90,91]

Adverse effects

Table 6 summarizes the adverse effects of single-agent vinorelbine in 327 patients with NSCLC or advanced breast cancer who were enrolled in one of three U.S. studies. In each study, vinorelbine was administered as a 30-mg/sq m i.v. infusion over 20 minutes weekly.

Hematologic toxicity. Granulocytopenia is the dose-limiting adverse effect of vinorelbine. Approximately two thirds of patients have had grade 3 or 4 granulocytopenia, 8% have required hospitalization because of fever or infection, and 1% have died of sepsis. The granulocytopenic nadir appears to occur 7–10 days after a dose; recovery typically occurs within the following 7–14 days. Clinical experience indicates that vinorelbine's effect on granulocytes is noncumulative. However, combination therapy with cisplatin appears to result in increased hematologic toxicity. In studies of oral vinorelbine, leukopenia was poorly correlated with C_{max} but well correlated with AUC, suggesting that total exposure to vinorelbine may be a more important factor in hematologic toxicity than peak concentration.[21]

Vinorelbine-induced anemia is common but rarely severe. In addition, platelets appear to be spared vinorelbine's toxic hematologic effects.

Liver enzymes. Transient increases in aspartate aminotransferase and alanine aminotransferase levels are common with vinorelbine. However, the increases are usually not severe and are generally asymptomatic.

Table 6.
Frequency of Adverse Effects in 327 Patients Receiving Vinorelbine Alone[a]

Adverse Effect	Frequency (%)		
	Overall	Grade 3	Grade 4
Bone marrow toxicity			
Granulocytopenia			
<2,000 granulocytes/cu mm	88	...	...
<500 granulocytes/cu mm	34	...	...
Leukopenia			
<4,000 leukocytes/cu mm	90	...	...
<1,000 leukocytes/cu mm	14	...	...
Thrombocytopenia			
<100,000 platelets/cu mm	3	...	...
<50,000 platelets/cu mm	1	...	...
Anemia			
Hemoglobin concentration, <11 g/dL	80	...	...
Hemoglobin concentration, <8 g/dL	9	...	...
Hospitalization due to granulocytopenic complications	7	...	...
Laboratory abnormalities			
Total bilirubin (n = 302)	10	4	2
Serum aspartate aminotransferase (n = 297)	62	3	1
General			
Asthenia	29	5	0
Injection-site reactions	26	2	0
Injection-site pain	13	2	0
Phlebitis	6	0	0
Digestive			
Nausea	38	2	0
Vomiting	17	2	0
Constipation	31	3	0
Diarrhea	15	1	0
Peripheral neuropathy	20	1	0
Dyspnea	5	2	0
Alopecia	10	0	0

[a]Adapted from package insert for vinorelbine (Navelbine, Glaxo Wellcome).

Alkaline phosphatase elevations are also common; however, these elevations probably reflect the high rate of liver and bone metastasis in the patient populations. A low rate of grade 3 or 4 elevation in bilirubin was seen in clinical trials.

General adverse events. Asthenia is one of the most common adverse effects of vinorelbine, occurring in one third of patients. The fatigue is generally mild or moderate but increases with repeated administration. Injection-site reactions are also frequent (26%) and primarily involve erythema, pain, vein discoloration, and phlebitis. The occurrence and severity of venous irritation appear to be reduced when vinorelbine is administered as a 6- to 10-minute infusion with a free-flowing i.v. fluid to ensure proper flushing of veins.[92] The frequency of phlebitis was notably greater in clinical trials in which vinorelbine was administered over one hour.[55,64] Like other vinca alkaloids, vinorelbine is a moderate vesicant; care must be used when administering vinorelbine through peripheral catheters. Extravasation reactions have not yet been reported in North America, but there have been reports in Europe. There is a French report of localized epidermal necrolysis after i.v. administration of vinorelbine.[93]

Cardiovascular toxicity. Chest pain has been reported in 5% of patients receiving vinorelbine. The majority of patients reporting chest pain have either a history of cardiovascular disease or a tumor within the chest. One report describes a fatal myocardial infarction in a patient with a previous infarction who received two courses of vinorelbine.[94] It is unclear what role vinorelbine played in the patient's myocardial infarction. Cardiovascular toxicity has been rarely reported with vincristine[95-97] and vinblastine.[98] The pathogenesis of cardiovascular toxicity is postulated to involve transitory coronary artery spasm.[97]

Gastrointestinal toxicity. Prophylactic antiemetic therapy has not been used routinely in clinical trials of vinorelbine. Nausea and vomiting occur in approximately 40% and 20% of patients, respectively. Vinorelbine-associated nausea and vomiting are typically mild to moderate and appear to respond to conventional antiemetic therapy; serotonin-receptor antagonists are generally not required. Diarrhea, anorexia, and stomatitis occur in less than 20% of patients and are rarely severe. Constipation occurs in one third of patients; paralytic ileus is noted in 2% of cases.

Neurologic toxicity. Vinorelbine appears to cause less neurotoxicity than the other vinca alkaloids. The most commonly reported neurologic adverse effect of vinorelbine is peripheral neuropathy manifested as paresthesia and hypesthesia. The frequency of peripheral neuropathy is 20%; there are very few reports of grade 3 or 4 toxicity. Loss of deep-tendon reflexes occurs in less than 5% of patients. In addition, tumor pain, jaw pain, and back pain (frequency unknown) have been reported; these reactions have also been reported in patients receiving other vinca alkaloids.[99]

The neurotoxic effects of vinorelbine seem to be reversible on discontinuation of drug. The addition of cisplatin does not appear to increase the neurotoxic effects of vinorelbine. However, prior treatment with paclitaxel may result in cumulative neurotoxicity.[100]

Dermatologic toxicity. Vinorelbine has caused alopecia, manifested as a gradual thinning of hair, in about 10% of patients. Few patients suffer total hair loss. Alopecia appears to be a cumulative toxicity of vinorelbine. Rashes are rare (4%).

Pulmonary toxicity. Shortness of breath has been noted in 5% of patients; 2% described severe shortness of breath. As with other vinca alkaloids, vinorelbine can produce both acute and subacute pulmonary reactions. The acute reaction resembles an allergic reaction and responds to bronchodilators. Subacute pulmonary reactions generally occur within one hour after drug administration and are characterized by cough, dyspnea, hypoxemia, and interstitial infiltration. Subacute reactions typically respond to corticosteroid therapy.

Pulmonary reactions have occurred with other vinca alkaloids, including vinblastine, in combination with mitomycin.[101]

Other. Hemorrhagic cystitis and the syndrome of inappropriate antidiuretic hormone secretion have been reported in less than 1% of patients treated with vinorelbine.

FDA-approved labeling

Vinorelbine carries FDA-approved labeling for use as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced NSCLC. Vinorelbine is indicated for use as a single agent or in combination with cisplatin in patients with stage IV disease. In stage III disease, vinorelbine is indicated for use in combination with cisplatin.

In June 1994, the FDA Oncology Drugs Advisory Committee voted against approving vinorelbine as a treatment for patients with metastatic breast cancer who have failed to respond to standard chemotherapy and for patients with metastatic breast cancer who have relapsed within six months after receiving an anthracycline-containing adjuvant regimen. There were several problems in the vinorelbine New Drug Application, including a nonstandard definition for time to disease progression, unplanned survival analysis, and missing documentation related to time to progression for a large number of patients. The committee asked the manufacturer to conduct an additional randomized trial of vinorelbine as a first-line agent to establish its value in breast cancer. Currently, vinorelbine plus doxorubicin is being compared with doxorubicin alone in 300–400 breast cancer patients being enrolled by the National Cancer Institute of Canada. The trial is expected to be completed in 1996.

Availability

Vinorelbine tartrate (Navelbine, Glaxo Wellcome) is supplied as a 10-mg/mL solution (of vinorelbine) in 1- and 5-mL vials. Vinorelbine can be administered by either slow i.v. push or i.v. infusion.[102] An oral formulation of vinorelbine remains under investigation.

Dosage

Standard dosage and modifications for toxicity. The recommended dosage of vinorelbine is 30 mg/sq m i.v. weekly. Because the drug undergoes substantial hepatic metabolism and biliary excretion, dosage adjustments are recommended for patients with hepatic insufficiency. The manufacturer recommends a dose of 15 mg/sq m for patients with a total bilirubin concentration of 2.1–3 mg/dL and 7.5 mg/sq m for patients with a total bilirubin concentration of greater than 3 mg/dL. Modifications in the dosage are also recommended in cases of hematologic toxicity. A dose of 15 mg/sq m is recommended for patients with granulocyte counts of 1000–1499 cells/cu mm. Vinorelbine should not be given to patients with a granulocyte count of less than 1000 cells/cu mm; vinorelbine treatment should be discontinued if the granulocyte count remains below 1000 cells/cu mm for more than three weeks. The manufacturer also recommends that patients who have fever or sepsis while they are granulocytopenic or who require two consecutive weekly postponements of administration due to prolonged granulocytopenia should receive 22.5 mg/sq m if the granulocyte count is greater than 1500 cells/cu mm and 11.25 mg/sq m if the count is 1000–1499 cells/cu mm. Vinorelbine should be discontinued if moderate or severe neurotoxicity develops during treatment. Firm evidence to support the necessity of dosage reductions is lacking, although the recommended dosage adjustments are consistent with those recommended for other vinca alkaloids.

Alternative dosage regimens. Although the FDA-approved dosage of vinorelbine is 30 mg/sq m i.v. weekly, it is uncertain if this regimen is optimal for clinical use. Weekly bolus doses are inconvenient and costly. Furthermore, the available evidence suggests that 30 mg/sq m may not be tolerated in the majority of patients, particularly those with metastatic breast cancer who have received previous chemotherapy. In such patients, lower doses or the addition of colony-stimulating factors may be necessary.

Investigation into novel dosage regimens designed to deliver vinorelbine at higher dose intensities has begun, and some preliminary results are encouraging. A modified dosage regimen was reported at a recent world conference on lung cancer.[103] With the knowledge that the combination of cisplatin and vinorelbine typically produces a nadir white blood cell count on day 15, the investigator gave patients with NSCLC vinorelbine 35 mg/sq m on days 1, 15, and 29, and 17.5 mg/sq m on days 8 and 22. This regimen resulted in an average 20% enhancement in the dose intensity of vinorelbine compared with standard dosage schemes.

Crawford and O'Rourke[104] reported an increased vinorelbine dose intensity when filgrastim was used with the combination of carboplatin and vinorelbine in patients with NSCLC. Previously there had been little experience with using a colony-stimulating factor to support patients receiving weekly chemotherapy regimens because of concern about a potential overlap between neutrophil recovery and the next chemotherapy treatment. These investigators conducted a Phase I study in 22 patients with stage IV NSCLC designed to determine the maximum tolerated dosage of vinorelbine when administered with filgrastim and a standard dose of carboplatin given on days 1 and 29. The patients received one of four dosages of vinorelbine ranging from 0 to 30 mg/sq m weekly. Specific criteria for administering filgrastim daily (except 24 hours before and 24 hours after antineoplastic administration) were

developed. The dose of filgrastim ranged from 1 to 5 µg/kg/day, depending on the neutrophil count before therapy began. Intensification of the dosage of vinorelbine plus carboplatin was possible, but full-dose therapy required filgrastim support in the majority of the patients. A Phase II study of this regimen is in progress.

Conclusion

In clinical studies, vinorelbine has shown activity against non-small-cell lung cancer both as a single agent and in combination with cisplatin. Vinorelbine plus cisplatin resulted in a higher response rate and longer survival than vindesine plus cisplatin, a combination previously found to be superior to best supportive care. But because a recent meta-analysis showed a minimal (six-week) gain in survival with chemotherapy compared with supportive care, the most appropriate method for determining if the vinorelbine–cisplatin combination is truly advantageous may be a direct comparison of the drug combination with supportive care. It is difficult to predict the future role for vinorelbine plus cisplatin in the treatment of non-small-cell lung cancer, since the response rate is 20–30%, the improvement in median survival time is only eight weeks, and the value of any chemotherapy in this disease is questionable. However, given the prevalence of non-small-cell lung cancer and the lack of effective treatments, the identification of any agent with significant activity is encouraging. Young patients with good performance status may gain the greatest benefit from vinorelbine. Vinorelbine has also shown promise in the treatment of several other types of tumors. In particular, response rates of about 30% to vinorelbine alone in previously treated breast-cancer patients, including patients who had received anthracycline-containing regimens, suggest that vinorelbine may have an emerging role in combination chemotherapy regimens for advanced breast cancer.

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